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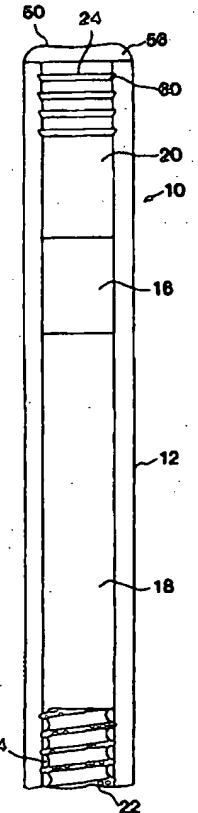
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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## (54) Title: SUSTAINED DELIVERY OF AN ACTIVE AGENT USING AN IMPLANTABLE SYSTEM

## (57) Abstract

The invention is directed to a device for delivering an active agent formulation for a predetermined administration period. An impermeable reservoir is divided into a water-swellable agent chamber and an active agent formulation chamber. Fluid from the environment is imbibed through a semipermeable plug into the water-swellable agent chamber and the active agent formulation is released through a back-diffusion regulating outlet. Delivery periods of up to 2 years are achieved.



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1                   **SUSTAINED DELIVERY OF AN ACTIVE AGENT USING AN**  
2                   **IMPLANTABLE SYSTEM**

3

4                   **Technical Field**

5

6                  This invention is related to the sustained delivery of a biologically  
7                  active agent. More particularly, the invention is directed to an implantable  
8                  delivery system for the prolonged delivery of an active agent to a fluid  
9                  environment in a natural or artificial body cavity.

10

11                  **Background of the Invention**

12

13                  Treatment of disease by prolonged delivery of an active agent at a  
14                  controlled rate has been a goal in the drug delivery field. Various approaches  
15                  have been taken toward delivering the active agents.

16                  One approach involves the use of implantable diffusional systems. For  
17                  example, subdermal implants for contraception are described by Philip D.  
18                  Darney in *Current Opinion in Obstetrics and Gynecology* 1991, 3:470-476.  
19                  Norplant® requires the placement of 6 levonorgestrel-filled silastic capsules  
20                  under the skin. Protection from conception for up to 5 years is achieved. The  
21                  implants operate by simple diffusion, that is, the active agent diffuses through  
22                  the polymeric material at a rate that is controlled by the characteristics of the  
23                  active agent formulation and the polymeric material. Darney further describes  
24                  biodegradable implants, namely Capranor™ and norethindrone pellets.  
25                  These systems are designed to deliver contraceptives for about one year and  
26                  then dissolve. The Capranor™ systems consist of poly( $\epsilon$ -caprolactone)  
27                  capsules that are filled with levonorgestrel and the pellets are 10% pure  
28                  cholesterol with 90% norethindrone.  
29                  Implantable infusion pumps have also been described for delivering  
30                  drugs by intravenous, intra-arterial, intrathecal, intraperitoneal, intraspinal and  
31                  epidural pathways. The pumps are usually surgically inserted into a

1 subcutaneous pocket of tissue in the lower abdomen. Systems for pain  
2 management, chemotherapy and insulin delivery are described in the *BBI*/  
3 *Newsletter*, Vol. 17, No. 12, pages 209-211, December 1994. These systems  
4 provide for more accurately controlled delivery than simple diffusional  
5 systems.

6 One particularly promising approach involves osmotically driven  
7 devices such as those described in U.S. Patent Nos. 3,987,790, 4,865,845,  
8 5,057,318, 5,059,423, 5,112,614, 5,137,727, 5,234,692 and 5,234,693  
9 which are incorporated by reference herein. These devices can be implanted  
10 into an animal to release the active agent in a controlled manner for a  
11 predetermined administration period. In general, these devices operate by  
12 imbibing fluid from the outside environment and releasing corresponding  
13 amounts of the active agent.

14 The above-described devices have been useful for delivering active  
15 agents to a fluid environment of use. Although these devices have found  
16 application for human and veterinary purposes, there remains a need for  
17 devices that are capable of delivering active agents, particularly potent  
18 unstable agents, reliably to a human being at a controlled rate over a  
19 prolonged period of time.

20

21 **Summary of the Invention**

22

23 Implantable osmotic systems for delivery of an active agent to an  
24 animal are well known. Adaptation of these systems for human use raises a  
25 number of difficult issues. The size of the device may need to be decreased  
26 for human implantation. The strength of the device must be sufficient to  
27 ensure a robust system. Accurate and reproducible delivery rates and  
28 durations must be ensured and the period from implantation to start-up of  
29 delivery must be minimized. The active agent must retain its purity and  
30 activity for extended periods of time at the elevated temperatures  
31 encountered in the body cavity.

1        Accordingly, in one aspect, the invention is a fluid-imbibing device for  
2        delivering an active agent formulation to a fluid environment of use. The  
3        device comprises a water-swellable, semipermeable material that is received  
4        in sealing relationship with the interior surface at one end of an impermeable  
5        reservoir. The device further contains an active agent to be displaced from  
6        the device when the water-swellable material swells.

7        In another aspect, the invention is directed to an implantable device for  
8        delivering an active agent to a fluid environment of use. The device  
9        comprises a reservoir and a back diffusion regulating outlet in a mating  
10      relationship. The flow path of the active agent comprises a pathway formed  
11      between the mating surfaces of the back diffusion regulating outlet and the  
12      reservoir.

13      In yet another aspect, the present invention is directed to a device for  
14      storing an active agent in a fluid environment of use during a predetermined  
15      administration period, the device comprising a reservoir containing an active  
16      agent. The reservoir is impermeable and formed at least in part from a  
17      metallic material. The portion of the reservoir contacting the active agent is  
18      non-reactive with the active agent, and is formed of a material selected from  
19      the group consisting of titanium and its alloys.

20      In a further aspect, the invention is an implantable fluid-imbibing active  
21      agent delivery system that comprises an impermeable reservoir. The  
22      reservoir contains a piston that divides the reservoir into an active agent  
23      containing chamber and a water-swellable agent containing chamber. The  
24      active agent containing chamber is provided with a back-diffusion regulating  
25      outlet. The water-swellable agent containing chamber is provided with a  
26      semipermeable plug. Either the plug or the outlet is releasable from the  
27      reservoir at an internal pressure that is lower than the maximum osmotic  
28      pressure generated by the water-swellable agent.

29      The invention is further directed to a fluid-imbibing implantable active  
30      agent delivery system where the time to start-up of delivery is less than 10%  
31      of the predetermined administration period.

1        In another aspect, the invention is directed to a method for preparing a  
2        fluid-imbibing implantable active agent delivery system. The method  
3        comprises injection molding a semipermeable plug into the end of an  
4        impermeable reservoir such that the plug is protected by the reservoir.

5        In still another aspect, the invention is directed to an impermeable  
6        active agent delivery system for delivering an active agent that is susceptible  
7        to degradation. The reservoir contains a piston that divides the reservoir into  
8        a water-swellable agent chamber and an active agent chamber. The open  
9        end of the water-swellable agent chamber contains a semipermeable  
10      membrane and the open end of the active agent chamber contains a back-  
11      diffusion regulating outlet. The system effectively seals the active agent  
12      chamber and isolates it from the environment of use.

13      In a further aspect, the invention is directed to a back-diffusion  
14      regulating outlet useful in an active agent delivery system. The outlet defines  
15      a flow path wherein the length, interior cross-sectional shape and area  
16      provide for an average linear velocity of active agent that is higher than the  
17      linear inward flow of fluid in the environment of use.

18      The invention is also directed to a semipermeable plug useful in an  
19      active agent delivery system. The plug is water-swellable and must expand  
20      linearly in the delivery system to commence pumping upon insertion of the  
21      system into the fluid environment of use.

22      The invention is further directed to implantable delivery systems useful  
23      for delivering leuprolide.

24

#### 25                  Description of the Drawings

26

27      The figures are not drawn to scale, but are set forth to illustrate various  
28      embodiments of the invention. Like numbers refer to like structures.

29      Figs. 1 and 2 are partial cross-sectional views of two embodiments of  
30      the delivery device of the invention.

1       Fig. 3 is an enlarged cross-sectional view of the back-diffusion  
2 regulating outlet of Fig. 1.

3       Fig. 4 is a graph that shows the effect of orifice diameter and length on  
4 drug diffusion.

5       Figs. 5, 6, 7 and 8 are enlarged cross-sectional views of further  
6 embodiments of the semipermeable plug end of the reservoir according to the  
7 invention.

8       Figs. 9, 10 and 11 are graphs of release rates for systems with  
9 leuprolide (Fig. 9) and with blue dye and with different membranes (Figs. 10  
10 and 11).

11

#### Detailed Description of the Invention

13

14       The present invention provides a device for the delivery of an active  
15 agent to a fluid environment of use in which the active agent must be  
16 protected from the fluid environment until it is delivered. Prolonged and  
17 controlled delivery is achieved.

18

#### Definitions

20

21       The term "active agent" intends the active agent(s) optionally in  
22 combination with pharmaceutically acceptable carriers and, optionally  
23 additional ingredients such as antioxidants, stabilizing agents, permeation  
24 enhancers, etc.

25       By a "predetermined administration period" is intended a period of  
26 greater than 7 days, often between about 30 days and 2 years, preferably  
27 greater than about 1 month and usually between about 1 month and 12  
28 months.

29       By the time to "start-up" of delivery is intended the time from insertion  
30 into the fluid environment of use until the active agent is actually delivered at  
31 a rate not less than approximately 70% of the intended steady-state rate.

1       The term "impermeable" intends that the material is sufficiently  
2       impermeable to environmental fluids as well as ingredients contained within  
3       the dispensing device such that the migration of such materials into or out of  
4       the device through the impermeable device is so low as to have substantially  
5       no adverse impact on the function of the device during the delivery period.

6       The term "semipermeable" intends that the material is permeable to  
7       external fluids but substantially impermeable to other ingredients contained  
8       within the dispensing device and the environment of use.

9       As used herein, the terms "therapeutically effective amount" or  
10      "therapeutically effective rate" refer to the amount or rate of the active agent  
11      needed to effect the desired biologic or pharmacologic effect.

12      The active agent delivery devices of the invention find use where the  
13      prolonged and controlled delivery of an active agent is desired. In many  
14      cases the active agent is susceptible to degradation if exposed to the  
15      environment of use prior to delivery and the delivery devices protect the agent  
16      from such exposure.

17      Fig. 1 shows one embodiment of the device according to the invention.  
18      In Fig. 1 a fluid-imbibing system 10 is shown that comprises an impermeable  
19      reservoir 12. The reservoir 12 is divided into two chambers by a piston 16.  
20      The first chamber 18 is adapted to contain an active agent and the second  
21      chamber 20 is adapted to contain a fluid-imbibing agent. A back-diffusion  
22      regulating outlet 22 is inserted into the open end of the first compartment 18  
23      and a water-swellable semipermeable plug 24 is inserted into the open end of  
24      the second chamber 20. In Fig. 1, the back-diffusion regulating outlet 22 is  
25      shown as a male threaded member in a mating relationship with the smooth  
26      interior surface of the reservoir 12 thereby forming therebetween helical flow  
27      path 34. The pitch (x), the amplitude (y), and the cross-sectional area and  
28      shape of the helical path 34 formed between the mating surfaces of the back-  
29      diffusion regulating outlet 22 and the reservoir 12 as shown in Fig. 3 are  
30      factors that affect both the efficiency of path 34 preventing back-diffusion of  
31      external fluid into the formulation in chamber 18 and the back pressure in the

1 device. The geometry of outlet 22 prevents water diffusion into the reservoir.  
2 In general, it is desired that these characteristics be selected so that the  
3 length of the helical flow path 34 and the velocity of flow of active agent  
4 therethrough is sufficient to prevent back-diffusion of external fluid through the  
5 flow path 34 without significantly increasing the back pressure, so that,  
6 following start-up, the release rate of the active agent is governed by the  
7 osmotic pumping rate.

8 Fig. 2 is a second embodiment of the device of the invention with a  
9 reservoir 12, piston 16 and plug 26. In this embodiment, the flow path 36 is  
10 formed between a threaded back-diffusion regulating outlet 40 and threads 38  
11 formed on the interior surface of the reservoir 12. The amplitudes of the  
12 threaded portions of the back-diffusion regulating outlet 40 and reservoir 12  
13 are different so that a flow path 36 is formed between the reservoir 12 and the  
14 back-diffusion regulating outlet 40.

15 The water-swellable semipermeable plugs 24 and 26 shown in Figs. 1  
16 and 2 respectively are inserted into the reservoir such that the reservoir wall  
17 concentrically surrounds and protects the plug. In Fig. 1, the top portion 50 of  
18 the plug 24 is exposed to the environment of use and may form a flanged end  
19 cap portion 56 overlaying the end of reservoir 12. The semipermeable plug  
20 24 is resiliently engaged with the interior surface of the reservoir 12 and in  
21 Fig. 1 is shown to have ridges 60 that serve to frictionally engage the  
22 semipermeable plug 24 with the interior of reservoir 12. In addition, the  
23 ridges 60 serve to produce redundant circumferential seals that function  
24 before the semipermeable plug 24 expands due to hydration. The clearance  
25 between ridges 60 and the interior surface of the reservoir 12 prevents  
26 hydration swelling from exerting stresses on the reservoir 12 that can result in  
27 tensile failure of the reservoir 12 or compression or shear failure of the plug  
28 24. Fig. 2 shows a second embodiment of the semipermeable plug 26 where  
29 the plug is injection molded into the top portion of the reservoir and where the  
30 top of the semipermeable plug 26 is flush with the top 62 of the reservoir 12.  
31 In this embodiment, the diameter of the plug is substantially less than the

1 diameter of the reservoir 12. In both embodiments the plugs 24 and 26 will  
2 swell upon exposure to the fluid in body cavity forming an even tighter seal  
3 with the reservoir 12.

4 The novel configurations of the components of the above-described  
5 embodiments provide for implantable devices that are uniquely suited for  
6 implantation into humans and can provide delivery devices which are capable  
7 of storing unstable formulations at body temperatures for extended periods of  
8 time, which devices have start-up times of less than 10% of the administration  
9 period and can be designed to be highly reliable and with predictable fail safe  
10 modes.

11 Reservoir 12 must be sufficiently strong to ensure that it will not leak,  
12 crack, break or distort so as to expel its active agent contents under stresses  
13 it would be subjected to during use while being impermeable. In particular, it  
14 should be designed to withstand the maximum osmotic pressure that could be  
15 generated by the water-swellable material in chamber 20. Reservoir 12 must  
16 also be chemically inert and biocompatible, that is, it must be non-reactive  
17 with the active agent formulation as well as the body. Suitable materials  
18 generally comprise a non-reactive polymer or a biocompatible metal or alloy.  
19 The polymers include acrylonitrile polymers such as acrylonitrile-butadiene-  
20 styrene terpolymer, and the like; halogenated polymers such as  
21 polytetrafluoroethylene, polychlorotrifluoroethylene, copolymer  
22 tetrafluoroethylene and hexafluoropropylene; polyimide; polysulfone;  
23 polycarbonate; polyethylene; polypropylene; polyvinylchloride-acrylic  
24 copolymer; polycarbonate-acrylonitrile-butadiene-styrene; polystyrene; and  
25 the like. The water vapor transmission rate through compositions useful for  
26 forming the reservoir are reported in *J. Pharm. Sci.*, Vol. 29, pp. 1634-37  
27 (1970), *Ind. Eng. Chem.*, Vol. 45, pp. 2296-2306 (1953); *Materials*  
28 *Engineering*, Vol. 5, pp. 38-45 (1972); *Ann. Book of ASTM Stds.*, Vol. 8.02,  
29 pp. 208-211 and pp. 584-587 (1984); and *Ind. and Eng. Chem.*, Vol. 49, pp.  
30 1933-1936 (1957). The polymers are known in the *Handbook of Common*  
31 *Polymers* by Scott and Roff, CRC Press, Cleveland Rubber Co., Cleveland,

1 OH. Metallic materials useful in the invention include stainless steel, titanium,  
2 platinum, tantalum, gold and their alloys as well as gold-plated ferrous alloys,  
3 platinum-plated ferrous alloys, cobalt-chromium alloys and titanium nitride  
4 coated stainless steel. A reservoir made from titanium or a titanium alloy  
5 having greater than 60%, often greater than 85% titanium is particularly  
6 preferred for the most size-critical applications, for high payload capability and  
7 for long duration applications and for those applications where the formulation  
8 is sensitive to body chemistry at the implantation site or where the body is  
9 sensitive to the formulation. Preferred systems maintain at least 70% active  
10 agent after 14 months at 37°C and have a shelf stability of at least about 9  
11 months, or more preferably at least about two years, at 2-8°C. Most  
12 preferably, systems may be stored at room temperature. In certain  
13 embodiments, and for applications other than the fluid-imbibing devices  
14 specifically described, where unstable formulations are in chamber 18,  
15 particularly protein and/or peptide formulations, the metallic components to  
16 which the formulation is exposed must be formed of titanium or its alloys as  
17 described above.

18 The devices of this invention provide a sealed chamber 18 which  
19 effectively isolates the formulation from the fluid environment. The reservoir  
20 12 is made of a rigid, impermeable and strong material. The water-swellable  
21 semipermeable plug 24 is of a lower durometer material and will conform to  
22 the shape of the reservoir to produce a liquid-tight seal with the interior of  
23 reservoir 12 upon wetting. The flow path 34 isolates chamber 18 from back-  
24 diffusion of environmental fluid. Piston 16 isolates chamber 18 from the  
25 environmental fluids that are permitted to enter chamber 20 through  
26 semipermeable plugs 24 and 26 such that, in use at steady-state flow, active  
27 agent is expelled through outlet 22 at a rate corresponding to the rate at  
28 which water from the environment flows into the water-swellable material in  
29 chamber 20 through semipermeable plugs 24 and 26. As a result, the plug  
30 and the active agent formulation will be protected from damage and their  
31 functionality will not be compromised even if the reservoir is deformed. In

1 addition, the use of sealants and adhesives will be avoided and the attendant  
2 issues of biocompatibility and ease of manufacture resolved.

3 Materials from which the semipermeable plug are made are those that  
4 are semipermeable and that can conform to the shape of the reservoir upon  
5 wetting and adhere to the rigid surface of the reservoir. The semipermeable  
6 plug expands as it hydrates when placed in a fluid environment so that a seal  
7 is generated between the mating surfaces of the plug and the reservoir. The  
8 strength of the seals between the reservoir 12 and the outlet 22 and the  
9 reservoir 12 and the plugs 24 and 26 can be designed to withstand the  
10 maximum osmotic pressure generated by the device. In a preferred  
11 alternative, the plugs 24 and 26 may be designed to withstand at least 10X  
12 the osmotic agent compartment 20 operating pressure. In a further  
13 alternative the plugs 24 and 26 may be releasable from the reservoir at an  
14 internal pressure that is lower than the pressure needed to release the back  
15 diffusion regulating outlet. In this fail safe embodiment, the water-swellable  
16 agent chamber will be opened and depressurized, thus avoiding dispelling  
17 the diffusion regulating outlet and attendant release of a large quantity of the  
18 active agent. In other cases, where a fail-safe system requires the release of  
19 the active agent formulation rather than the water-swellable agent  
20 formulation, the semipermeable plug must be releasable at a pressure that is  
21 higher than the outlet.

22 In either case, the semipermeable plug must be long enough to  
23 sealably engage the reservoir wall under the operating conditions, that is, it  
24 should have an aspect ratio of between 1:10 and 10:1 length to diameter,  
25 preferably at least about 1:2 length to diameter, and often between 7:10 and  
26 2:1. The plug must be able to imbibe between about 0.1% and 200% by  
27 weight of water. The diameter of the plug is such that it will sealingly fit inside  
28 the reservoir prior to hydration as a result of sealing contact at one or more  
29 circumferential zones and will expand in place upon wetting to form an even  
30 tighter seal with the reservoir. The polymeric materials from which the  
31 semipermeable plug may be made vary based on the pumping rates and

1 device configuration requirements and include but are not limited to  
2 plasticized cellulosic materials, enhanced polymethylmethacrylate such as  
3 hydroxyethylmethacrylate (HEMA) and elastomeric materials such as  
4 polyurethanes and polyamides, polyether-polyamide copolymers,  
5 thermoplastic copolymers and the like.

6 The piston 16 isolates the water-swellable agent in chamber 20 from  
7 the active agent in chamber 18 and must be capable of sealably moving  
8 under pressure within reservoir 12. The piston 16 is preferably made of a  
9 material that is of lower durometer than the reservoir 12 and that will deform  
10 to fit the lumen of the reservoir to provide a fluid-tight compression seal with  
11 the reservoir 12. The materials from which the piston are made are  
12 preferably elastomeric materials that are impermeable and include but are not  
13 limited to polypropylene, rubbers such as EPDM, silicone rubber, butyl  
14 rubber, and the like, and thermoplastic elastomers such as plasticized  
15 polyvinylchloride, polyurethanes, Santoprene<sup>®</sup>, C-Flex<sup>®</sup> TPE (Consolidated  
16 Polymer Technologies Inc.), and the like. The piston may be of a self-loading  
17 or compression-loaded design.

18 The back-diffusion regulating outlet 22 forms the delivery pathway  
19 through which the active agent flows from the chamber 18 to the implantation  
20 site where absorption of the active agent takes place. The seal between the  
21 outlet 22 and the reservoir 12 can be designed to withstand the maximum  
22 osmotic pressure generated within the device or to fail-safe in the modes  
23 described above. In a preferred embodiment, the pressure required to  
24 release back-diffusion regulating outlet 22 is at least 10X the pressure  
25 required to move piston 16 and/or at least 10X the pressure in chamber 18.

26 The exit flow path of the active agent is the pathway 34 formed  
27 between the mating surfaces of the back-diffusion regulating outlet 22 and the  
28 reservoir 12. The pathway length, interior cross-sectional shape and area of  
29 the outlet path 34 or 36 are chosen such that the average linear velocity of  
30 the exiting active agent is higher than that of the linear inward flux of materials  
31 in the environment of use due to diffusion or osmosis, thereby attenuating or

12

1 moderating back-diffusion and its deleterious effects of contaminating the  
2 interior of the pump, destabilizing, diluting, or otherwise altering the  
3 formulation. The release rate of active agent can be modified by modifying  
4 the outlet pathway geometry, which relationship is shown below.

5 The convective flow of active agent out of outlet 22 is set by the  
6 pumping rate of the system and the concentration of active agent in chamber  
7 20 and can be represented as follows:

8

9                    $Q_{ca} = (Q) (C_a)$          (1)

10 where

11                    $Q_{ca}$  is the convective transport of agent A in mg/day

12                   Q is the overall convective transport of the agent and its  
13 diluents in cm<sup>3</sup>/day

14                    $C_a$  is the concentration of agent A in the formulation within  
15 chamber 20 in mg/cm<sup>3</sup>

16

17 The diffusive flow of agent A through the material in the outlet 22 is a  
18 function of agent concentration, cross-sectional configuration of flow path 34  
19 or 36, agent diffusivity and length of flow path 34 or 36, and can be  
20 represented as follows:

21

22                    $Q_{da} = D \pi r^2 \Delta C_a / L$          (2)

23 where

24                    $Q_{da}$  is the diffusive transport of agent A in mg/day

25                   D is the diffusivity through the material in path 34 or 36 in  
26 cm<sup>2</sup>/day

27                   r is the effective inner radius of the flow path in cm

28                    $\Delta C_a$  is the difference between the concentration of agent A in  
29 the reservoir and in the body outside of the outlet 22 in  
30 mg/cm<sup>3</sup>

31                   L is the length of the flow path in cm

In general, the concentration of agent in the reservoir is much greater than the concentration of agent in the body outside of the orifice such that the difference,  $\Delta C_a$  can be approximated by the concentration of agent within the reservoir,  $C_a$ .

$$Q_{da} = D \pi r^2 C_a / L \quad (3)$$

9 It is generally desirable to keep the diffusive flux of agent at less than  
10 10% of the convective flow. This is represented as follows:

$$Q_{da}/Q_{ca} = D \pi r^2 C_a / Q C_a L = D \pi r^2 / Q L \leq 0.1 \quad (4)$$

14 Equation 4 indicates that the relative diffusive flux decreases with  
15 increasing volumetric flow rate and path length and increases with increasing  
16 diffusivity and channel radius and is independent of drug concentration.  
17 Equation 4 is plotted in Figure 4 as a function of length (L) and diameter (d)  
18 for  $D = 2 \times 10^{-6} \text{ cm}^2/\text{sec}$  and  $Q = 0.36 \mu\text{l/day}$ .

The diffusive flux of water where the orifice opens into chamber 18  
can be approximated as:

$$Q_{wd}(\text{res}) = C_o Q_e e^{(-QL/D_w A)} \quad (5)$$

23 where

24  $C_o$  is the concentration profile of water in mg/cm<sup>3</sup>

25 Q is the mass flow rate in mg/day.

26 L is the length of the flow path in cm

27  $D_w$  is the diffusivity of water through the material in the flow path in  
28  $\text{cm}^2/\text{day}$

29 A is the cross-sectional area of the flow path in  $\text{cm}^2$

1        The hydrodynamic pressure drop across the orifice can be calculated  
 2        as follows:

$$3 \quad 4 \quad \Delta P = \frac{8 Q L \mu}{\pi r^4} \quad (6)$$

6        7        Simultaneously solving equations (4), (5) and (6) gives the values  
 8        shown in Table 1 where:

10	Q	= 0.38 $\mu$ l/day
11	C <sub>a</sub>	= 0.4 mg/ $\mu$ l
12	L	= 5 cm
13	D <sub>a</sub>	= 2.00 E-06 cm <sup>2</sup> /sec
14	$\mu$	= 5.00 E + 02 cp
15	C <sub>w0</sub>	= 0 mg/ $\mu$ l
16	D <sub>w</sub>	= 6.00 E + 06 cm <sup>2</sup> /sec

19        Table 1

Effective Orifice dia (mil)	Cross Sec area (mm <sup>2</sup> )	Drug Diffusion & Pumping			Water Intrusion		Pressure Drop psi
		Pump rate QC <sub>a</sub> mg/day	Diffusion QD <sub>a</sub> mg/day	Diff/Conv QD <sub>a</sub> /QC <sub>a</sub>	QD <sub>w</sub> mg/day	Qdw mg/year	
1	0.00051	0.152	0.0001	0.0005	0	0	1.55800
2	0.00203	0.152	0.0003	0.0018	1.14E-79	4.16E-77	0.09738
3	0.00456	0.152	0.0006	0.0041	4.79E-36	1.75E-33	0.01923
4	0.00811	0.152	0.0011	0.0074	8.89E-21	3.25E-18	0.00609
5	0.01267	0.152	0.0018	0.0115	1.04E-13	3.79E-11	0.00249
6	0.01824	0.152	0.0025	0.0166	7.16E-10	2.61E-07	0.00120
7	0.02483	0.152	0.0034	0.0226	1.48E-07	5.4E-05	0.00065
8	0.03243	0.152	0.0045	0.0295	4.7E-06	0.001715	0.00038
9	0.04105	0.152	0.0057	0.0373	5.04E-05	0.018381	0.00024
10	0.05068	0.152	0.0070	0.0461	0.000275	0.100263	0.00016
11	0.06132	0.152	0.0085	0.0558	0.000964	0.351771	0.00011
12	0.07298	0.152	0.0101	0.0664	0.002504	0.913839	0.00008
13	0.08564	0.152	0.0118	0.0779	0.005263	1.921027	0.00005
14	0.09933	0.152	0.0137	0.0903	0.00949	3.463836	0.00004
15	0.11402	0.152	0.0158	0.1037	0.015269	5.573195	0.00003
16	0.12973	0.152	0.0179	0.1180	0.022535	8.225224	0.00002
17	0.14646	0.152	0.0202	0.1332	0.031114	11.35656	0.00002
18	0.16419	0.152	0.0227	0.1493	0.040772	14.88166	0.00001
19	0.18295	0.152	0.0253	0.1664	0.051253	18.70728	0.00001
20	0.20271	0.152	0.0280	0.1844	0.062309	22.7427	0.00001

1       The calculations indicate that an orifice diameter of between about 3  
2       and 10 mil and a length of 2 to 7 cm is optimal for a device with the operating  
3       conditions described. In a preferred embodiment, the pressure drop across  
4       the orifice is less than 10% of the pressure required to release the back-  
5       diffusion regulating outlet 22.

6       The back-diffusion regulating outlet 22 preferably forms a helical  
7       pathway 34 or 36 incorporating a long flow path with a means of mechanically  
8       attaching the outlet into the reservoir without using adhesives or other  
9       sealants. The back-diffusion regulating outlet is made of an inert and  
10      biocompatible material selected from but not limited to metals including but  
11      not limited to titanium, stainless steel, platinum and their alloys and cobalt-  
12      chromium alloys and the like, and polymers including but not limited to  
13      polyethylene, polypropylene, polycarbonate and polymethylmethacrylate and  
14      the like. The flow path is usually between about 0.5 and 20 cm long,  
15      preferably between about 1 and 10 cm long and between about 0.001 and  
16      0.020 inches in diameter, preferably between about 0.003 and 0.015 inches  
17      to allow for a flow of between about 0.02 and 50  $\mu\text{l}/\text{day}$ , usually 0.2 to 10  
18       $\mu\text{l}/\text{day}$  and often 0.2 to 2.0  $\mu\text{l}/\text{day}$ . Additionally, a catheter or other system  
19      may be attached to the end of the back-diffusion regulating outlet to provide  
20      for delivery of the active agent formulation at a site removed from the implant.  
21      Such systems are known in the art and are described, for example, in U.S.  
22      Patent Nos. 3,732,865 and 4,340,054 which are incorporated herein by  
23      reference. Further, the flow path design may be useful in systems other than  
24      the fluid-imbibing devices specifically described herein.

25      The inventive device configurations described above also allow for a  
26      minimal period of delay from start-up to steady-state flow rate. This is  
27      accomplished in part as a result of the configuration of the semipermeable  
28      plug 24 or 26. As water is imbibed by the semipermeable plug, it swells.  
29      Radial expansion is limited by the rigid reservoir 12, thus the expansion must  
30      occur linearly, thereby pushing against the water-swellable agent in chamber  
31      18, which in turn pushes against the piston 16. This allows pumping to

1 commence prior to the time that water reaches the water-swellable agent  
2 which otherwise would be required before pumping could commence. To  
3 facilitate reliable start-up, the flow path 34 can be precharged with the active  
4 agent in chamber 18. Further, the geometry of the outlet 22 allows for initial  
5 delivery that is influenced by the concentration gradient of drug along the  
6 length of the outlet. The start-up period is less than about 25% of the  
7 predetermined delivery period and is often less than about 10% and usually  
8 less than about 5% of the predetermined delivery period. In a preferred  
9 embodiment for a one year system, at least 70% of the steady-state flow rate  
10 is achieved by day 14.

11 The water-swellable agent formulation in chamber 20 is preferably a  
12 tissue tolerable formulation whose high osmotic pressure and high solubility  
13 propels the active agent over a long period of time while remaining in  
14 saturated solution in the water admitted by the semipermeable membrane.  
15 The water-swellable agent is preferably selected for tolerability by  
16 subcutaneous tissue, at least at pumping rates and hypothetically resulting  
17 concentrations to allow inadvertent dispensing from implanted devices left in  
18 the patient for a longer than labeled period. In preferred embodiments, the  
19 water-swellable agent should not diffuse or permeate through the  
20 semipermeable plug 24 or 26 to any appreciable amount (e.g., less than 8%)  
21 under normal operating conditions. Osmotic agents, such as NaCl with  
22 appropriate tabletting agents (lubricants and binders) and viscosity modifying  
23 agents, such as sodium carboxymethylcellulose or sodium polyacrylate are  
24 preferred water-swellable agents. Other osmotic agents useful as the water-  
25 swellable agent include osmopolymers and osmagents and are described, for  
26 example, in U.S. Patent No. 5,413,572 which is incorporated by reference  
27 herein. The water-swellable agent formulation can be a slurry, a tablet, a  
28 molded or extruded material or other form known in the art. A liquid or gel  
29 additive or filler may be added to chamber 20 to exclude air from spaces  
30 around the osmotic engine. Exclusion of air from the devices should mean

1 that delivery rates will be less affected by nominal external pressure changes  
2 (e.g.,  $\pm 7$  p.s.i. ( $\pm 5$  a.t.m.)).

3 The devices of the invention are useful to deliver a wide variety of  
4 active agents. These agents include but are not limited to pharmacologically  
5 active peptides and proteins, genes and gene products, other gene therapy  
6 agents, and other small molecules. The polypeptides may include but are not  
7 limited to growth hormone, somatotropin analogues, somatomedin-C,  
8 Gonadotropic releasing hormone, follicle stimulating hormone, luteinizing  
9 hormone, LHRH, LHRH analogues such as leuprolide, nafarelin and  
10 goserelin, LHRH agonists and antagonists, growth hormone releasing factor,  
11 calcitonin, colchicine, gonadotropins such as chorionic gonadotropin,  
12 oxytocin, octreotide, somatotropin plus an amino acid, vasopressin,  
13 adrenocorticotropic hormone, epidermal growth factor, prolactin,  
14 somatostatin, somatotropin plus a protein, cosyntropin, lypressin,  
15 polypeptides such as thyrotropin releasing hormone, thyroid stimulation  
16 hormone, secretin, pancreozymin, enkephalin, glucagon, endocrine agents  
17 secreted internally and distributed by way of the bloodstream, and the like.  
18 Further agents that may be delivered include  $\alpha$ , antitrypsin, factor VIII, factor  
19 IX and other coagulation factors, insulin and other peptide hormones, adrenal  
20 cortical stimulating hormone, thyroid stimulating hormone and other pituitary  
21 hormones, interferon  $\alpha$ ,  $\beta$ , and  $\delta$ , erythropoietin, growth factors such as  
22 GCSF, GMCSF, insulin-like growth factor 1, tissue plasminogen activator,  
23 CD4, dDAVP, interleukin-1 receptor antagonist, tumor necrosis factor,  
24 pancreatic enzymes, lactase, cytokines, interleukin-1 receptor antagonist,  
25 interleukin-2, tumor necrosis factor receptor, tumor suppresser proteins,  
26 cytotoxic proteins, and recombinant antibodies and antibody fragments, and  
27 the like.

28 The above agents are useful for the treatment of a variety of conditions  
29 including but not limited to hemophilia and other blood disorders, growth  
30 disorders, diabetes, leukemia, hepatitis, renal failure, HIV infection, hereditary  
31 diseases such as cerbrosidase deficiency and adenosine deaminase

1 deficiency, hypertension, septic shock, autoimmune diseases such as  
2 multiple sclerosis, Graves disease, systemic lupus erythematosus and  
3 rheumatoid arthritis, shock and wasting disorders, cystic fibrosis, lactose  
4 intolerance, Crohn's diseases, inflammatory bowel disease, gastrointestinal  
5 and other cancers.

6 The active agents may be anhydrous or aqueous solutions,  
7 suspensions or complexes with pharmaceutically acceptable vehicles or  
8 carriers such that a flowable formulation is produced that may be stored for  
9 long periods on the shelf or under refrigeration, as well as stored in an  
10 implanted delivery system. The formulations may include pharmaceutically  
11 acceptable carriers and additional inert ingredients. The active agents may  
12 be in various forms, such as uncharged molecules, components of molecular  
13 complexes or pharmacologically acceptable salts. Also, simple derivatives of  
14 the agents (such as prodrugs, ethers, esters, amides, etc.) which are easily  
15 hydrolyzed by body pH, enzymes, etc., can be employed.

16 It is to be understood that more than one active agent may be  
17 incorporated into the active agent formulation in a device of this invention and  
18 that the use of the term "agent" in no way excludes the use of two or more  
19 such agents. The dispensing devices of the invention find use, for example,  
20 in humans or other animals. The environment of use is a fluid environment  
21 and can comprise any subcutaneous position or body cavity, such as the  
22 peritoneum or uterus, and may or may not be equivalent to the point of  
23 ultimate delivery of the active agent formulation. A single dispensing device  
24 or several dispensing devices can be administered to a subject during a  
25 therapeutic program. The devices are designed to remain implanted during a  
26 predetermined administration period. If the devices are not removed following  
27 the administration, they may be designed to withstand the maximum osmotic  
28 pressure of the water-swellable agent or they may be designed with a bypass  
29 to release the pressure generated within the device.

30 The devices of the present invention are preferably rendered sterile  
31 prior to use, especially when such use is implantation. This may be

1       accomplished by separately sterilizing each component, e.g., by gamma  
2       radiation, steam sterilization or sterile filtration, then aseptically assembling  
3       the final system. Alternatively, the devices may be assembled, then  
4       terminally sterilized using any appropriate method.

5

6       Preparation of the Devices of the Invention

7

8       Reservoir 12 is prepared preferably by machining a metal rod or by  
9       extrusion or injection molding a polymer. The top portion of the reservoir may  
10      be open as shown in Fig. 1 or may contain a cavity as shown in Fig. 2.

11      Where the reservoir 12 is open as shown in Fig. 1, a water-swellable  
12      semipermeable plug 24 is inserted mechanically from the outside of the  
13      reservoir without using an adhesive before or after insertion of the piston and  
14      water-swellable agent formulation. Reservoir 12 may be provided with  
15      grooves or threads which engage ribs or threads on plug 24.

16      Where the reservoir 12 contains a cavity as shown in Fig. 2, the cavity  
17      may be cylindrical in shape, as shown in Fig. 5, it may be stepped, as shown  
18      in Fig. 6, it may be helical, as shown in Fig. 7 or it may be in a spaced  
19      configuration, as shown in Fig. 8. The semipermeable plug 26 is then  
20      injected, inserted, or otherwise assembled into the cavity so that it forms a  
21      seal with the reservoir wall.

22      Following insertion of the plug 26 either mechanically, by welding or by  
23      injection, the water-swellable agent is assembled into the reservoir followed  
24      by insertion of the piston, with appropriate steps taken to vent entrapped air.  
25      The active agent is filled into the device using a syringe or a precision  
26      dispensing pump. The diffusion moderator is inserted into the device, usually  
27      by a rotating or helical action, or by axial pressing.

28      The following examples are illustrative of the present invention. They  
29      are not to be construed as limiting the scope of the invention. Variations and  
30      equivalents of these examples will be apparent to those of skill in the art in  
31      light of the present disclosure, the drawings and claims herein.

1

2

Examples

3

## 4        Example 1 - Preparation of a Device with an HDPE Reservoir

5

6        A system containing leuprolide acetate for the treatment of prostate  
7        cancer was assembled from the following components:

8              Reservoir (HDPE) (5 mm outside diameter, 3 mm inside diameter)

9              Piston (Santoprene®)

10          Lubricant (silicone medical fluid)

11          Compressed osmotic engine (60% NaCl, 40% sodium carboxymethyl  
12              cellulose)13          Membrane plug (Hytrel polyether-ester block copolymer, injection  
14              molded to desired shape)

15          Back diffusion Regulating Outlet (polycarbonate)

16          Active agent (0.78g of 60% propylene glycol and 40% leuprolide  
17              acetate)18        Assembly

19        The piston and inner diameter of the reservoir were lightly lubricated  
20        with silicon medical fluid. The piston 16 was inserted into the open end of  
21        chamber 20. Two osmotic engine tablets (40 mg each) were then inserted on  
22        top of piston 16. After insertion, the osmotic engine was flush with the end of  
23        the reservoir. The membrane plug 24 was inserted by lining up the plug with  
24        the reservoir and pushing gently until the plug was fully engaged in the  
25        reservoir. Active agent was loaded into a syringe which was then used to fill  
26        chamber 18 from its open end by injecting the material into the open tube until  
27        the formulation was ~3 mm from the end. The filled reservoir was centrifuged  
28        (outlet end "up") to remove any air bubbles that have been trapped in the  
29        formulation during filling. The outlet 22 was screwed into the open end of the  
30        reservoir until completely engaged. As the outlet was screwed in, excess  
31        formulation exited out of the orifice ensuring a uniform fill.

1

## 2           Example 2 - Insertion of the Device of Example 1

3

4           Insertion of the device of Example 1 is done under aseptic conditions  
5       using a trocar similar to that used in the implantation of Norplant®  
6       contraceptive implants to position the device under the skin. The insertion  
7       area is typically in the inside of the upper arm, 8 to 10 cm above the elbow.

8           The area is anesthetized and an incision is made through the skin.

9       The incision is approximately 4 mm long. The trocar is inserted into the  
10      incision until the tip of the trocar is at a distance of 4 to 6 cm from the incision.

11       The obturator is then removed from the trocar and the device of Example 1  
12      inserted into the trocar. The device is then advanced to the open end of the  
13      trocar using the obturator. The obturator is then held in position, thus  
14      immobilizing the device of Example 1 while the trocar is withdrawn over both  
15      the device and the obturator. The obturator is then removed, leaving the  
16      implant behind in a well-controlled position. The edges of the incision are  
17      then secured with a skin closure. The area is covered and kept dry for 2 to 3  
18      days.

19

## 20           Example 3 - Removal of the Device of Example 1

21

22       The device of Example 1 is removed as follows: The device is located  
23      by fingertip palpation of the upper arm area. The area at one end of the  
24      implant is then anesthetized and an approximately 4 mm, perpendicular  
25      incision is made through the skin and any fibrous capsule tissue surrounding  
26      the implant area. The end of the device opposite the incision is pushed so  
27      that the device end proximal to the incision is urged out of the incision. Any  
28      further fibrotic tissue is cut with a scalpel. Following removal, the procedure  
29      of Example 2 can be followed to insert a new device.

## 1                   Example 4 - Delivery Rate of the Device of Example 1

2

3                   Glass test tubes were filled with 35 ml distilled water and then placed  
4                   in a 37°C water bath. A single device as described in Example 1 was placed  
5                   in each test tube and the test tubes were changed periodically. The delivery  
6                   rate profile from the system is shown in Fig. 9. The system does not have  
7                   any start-up time because the system exhibits a period of initial high release  
8                   followed by a lower steady state release for a period of 200 days.

9

## 10                  Example 5 - Delivery Rate Profiles

11

12                  Glass test tubes were filled with 35 ml distilled water which were then  
13                  placed in a 37°C water bath. After the test tubes had come up to  
14                  temperature, a single device as described in Example 1, but with membrane  
15                  materials described below and containing 1% FD&C blue dye in water as the  
16                  drug formulation, was placed in each tube. Water from the test tube  
17                  permeated through the membrane causing the system to pump formulation  
18                  (blue dye) into the surrounding water in the test tube. At regular intervals,  
19                  systems were switched to fresh test tubes. The amount of dye released was  
20                  determined by measuring the concentration of blue dye in each test tube  
21                  using a spectrophotometer. The pumping rate was calculated from the total  
22                  dye released, the volume of water in the tube, the initial concentration of dye  
23                  and the interval over which the system was in the test tube. Results for two  
24                  different tests are shown in Figures 10 and 11. Figure 10 shows 3 different  
25                  systems with different plug materials (Hytrel® 2, 3 and 12 month systems) and  
26                  Figure 11 shows 4 systems with different plug materials. These materials are:

27	<u>Membrane</u>	<u>Material</u>
28	1 month	Pebax 25 (Polyamide)
29	2 month	Pebax 22 (Polyamide)
30	3 month	Polyurethane (HP60D)
31	12 month	Pebax 24 (Polyamide)

1       The systems were capable of delivering for a period of from 2 to 12  
2 months, depending on the membrane used.

3

4       **Example 6 - Preparation of a Delivery Device with a Titanium Reservoir**

5  
6       A system containing leuprolide acetate for the treatment of prostate  
7 cancer was assembled from the following components:

8       Reservoir (Titanium, Ti6Al4V alloy ) (4 mm outside diameter, 3 mm  
9                    inside diameter)

10      Piston (C-Flex<sup>®</sup>)

11      Lubricant (silicone medical fluid)

12      Compressed osmotic engine (76.4% NaCl, 15.5% sodium  
13                    carboxymethyl cellulose, 6% povidone, 0.5% Mg Stearate, 1.6%  
14                    water)

15      PEG 400 (8 mg added to osmotic engine to fill air spaces)

16      Membrane plug (polyurethane polymer, injection molded to desired  
17                    shape)

18      Back diffusion Regulating Outlet (polyethylene)

19      Drug formulation (0.150g of 60% water and 40% leuprolide acetate)

20      Assembly

21      The piston and inner diameter of the reservoir were lightly lubricated.

22      The piston was inserted ~0.5 cm into the reservoir at the membrane end.

23      PEG 400 was added into the reservoir. Two osmotic engine tablets (40 mg  
24      each) were then inserted into the reservoir from the membrane end. After  
25      insertion, the osmotic engine was flush with the end of the reservoir. The  
26      membrane plug was inserted by lining up the plug with the reservoir and  
27      pushing gently until the retaining features of the plug were fully engaged in  
28      the reservoir. Formulation was loaded into a syringe which was then used to  
29      fill the reservoir from the outlet end by injecting formulation into the open tube  
30      until the formulation was ~3 mm from the end. The filled reservoir was  
31      centrifuged (outlet end "up") to remove any air bubbles that have been

1       trapped in the formulation during filling. The outlet was screwed into the open  
2       end of the reservoir until completely engaged. As the outlet was screwed in,  
3       excess formulation exited out of the orifice ensuring a uniform fill.

4

5       **Example 7 - Preparation of a Leuprolide Acetate Delivery Device with a**  
6       **Titanium Reservoir**

7

8       A system containing leuprolide acetate for the treatment of prostate  
9       cancer was assembled from the following components:

10      Reservoir (Titanium Ti6Al4V alloy) (4 mm outside diameter, 3 mm  
11        inside diameter, 4.5 cm length)

12      Piston (C-Flex® TPE elastomer, available from Consolidated Polymer  
13        Technologies, Inc.)

14      Lubricant (silicone medical fluid 360)

15      Compressed osmotic engine tablet (76.4% NaCl, 15.5% sodium  
16        carboxymethyl cellulose, 6% povidone, 0.5% Mg Stearate, 1.5%  
17        water, 50 mg total)

18      PEG 400 (8 mg added to osmotic engine to fill air spaces)

19      Membrane plug (polyurethane polymer 20% water uptake, injection  
20        molded to desired shape 3 mm diameter X 4 mm length)

21      Back-diffusion Regulating Outlet (polyethylene, with 6 mil X 5 cm  
22        channel)

23      Drug formulation (leuprolide acetate dissolved in DMSO to a measured  
24        content of 65 mg leuprolide)

25      Assembly

26      Systems were assembled as in Example 6, using aseptic procedures  
27      to assemble  $\gamma$ -irradiated subassemblies and filled aseptically with sterile  
28      filtered leuprolide DMSO formulation.

29      Release Rate

30      These systems delivered about 0.35  $\mu$ L/day leuprolide formulation  
31      containing on average 150  $\mu$ g leuprolide in the amount delivered per day.

1 They provide delivery of leuprolide at this rate for at least one year. The  
2 systems achieved approximately 70% steady-state delivery by day 14.

3 Implantation and Removal

4 Systems will be implanted under local anesthetic and by means of an  
5 incision and trocar as in Example 2 to patient suffering from advanced  
6 prostatic cancer.

7 After one year, systems will be removed under local anesthetic as  
8 described in Example 3. New systems may be inserted at that time.

9

10                   **Example 8 - Treatment of Prostatic Cancer**

11

12                  Leuprolide acetate, an LHRH agonist, acts as a potent inhibitor of  
13 gonadotropin secretion when given continuously and in therapeutic doses.  
14 Animal and human studies indicate that following an initial stimulation, chronic  
15 administration of leuprolide acetate results in suppression of testicular  
16 steroidogenesis. This effect is reversible upon discontinuation of drug  
17 therapy. Administration of leuprolide acetate has resulted in inhibition of the  
18 growth of certain hormone-dependent tumors (prostatic tumors in Noble and  
19 Dunning male rats and DMBA-induced mammary tumors in female rats) as  
20 well as atrophy of the reproductive organs. In humans, administration of  
21 leuprolide acetate results in an initial increase in circulating levels of  
22 luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a  
23 transient increase in levels of the gonadal steroids (testosterone and  
24 dihydrotestosterone in males). However, continuous administration of  
25 leuprolide acetate results in decreased level of LH and FSH. In males,  
26 testosterone is reduced to castrate levels. These decreases occur within two  
27 to six weeks after initiation of treatment, and castrate levels of testosterone in  
28 prostatic cancer patients have been demonstrated for multiyear periods.  
29 Leuprolide acetate is not active when given orally.

- 1        Systems will be prepared as in Example 7, then inserted as described.
- 2        The continuous administration of leuprolide for one year using these systems
- 3        will reduce testosterone to castrate levels.
- 4        The above description has been given for ease of understanding only.
- 5        No unnecessary limitations should be understood therefrom, as modifications
- 6        will be obvious to those skilled in the art.

1    We claim:

2

3        1. A fluid-imbibing device for delivering an active agent to a fluid  
4        environment of use, said device comprising a water-swellable semipermeable  
5        material that is received in sealing relationship with the interior surface of one  
6        end of an impermeable reservoir and an active agent to be displaced from the  
7        device when the water-swellable material swells.

8

9        2. The device of claim 1 wherein the aspect ratio of the plug is  
10      1:10 to 10:1 length to diameter.

11

12      3. The device of claim 1 wherein the semipermeable material is  
13      assembled into an open end of the reservoir.

14

15      4. The device of claim 1 wherein the semipermeable material is  
16      assembled into a cavity in said reservoir.

17

18      5. The device of claim 4 wherein the cavity is of a shape selected  
19      from the group consisting of a cylindrical, stepped, helical threaded and  
20      spaced configuration.

21

22      6. An implantable device for delivering an active agent to a fluid  
23      environment of use, said device comprising a reservoir and a back-diffusion  
24      regulating outlet in mating relationship, wherein a flow path for the active  
25      agent comprises a pathway formed between the mating surfaces of the  
26      reservoir and the back-diffusion regulating outlet.

27

28      7. The device of claim 6 where the active agent is delivered at a  
29      rate of 0.02 to 50  $\mu$ l/day.

30

1       8. A device for storing an active agent in a fluid environment of use  
2       during a predetermined administration period, the device comprising a  
3       reservoir containing an active agent, said reservoir being formed at least in  
4       part from a metallic material, the portion of said reservoir contacting said  
5       active agent being non-reactive with the active agent, said metallic material in  
6       contact with active agent being formed of a material selected from the group  
7       consisting of titanium and its alloys.

8

9       9. The device of claim 8 wherein the titanium alloy is at least 60%  
10      titanium.

11

12       10. An implantable fluid-imbibing active agent delivery system  
13       comprising an impermeable reservoir and containing a piston that divides the  
14       reservoir into an active agent containing chamber and a water-swellable  
15       agent containing chamber, wherein the active agent containing chamber is  
16       provided with a back-diffusion regulating outlet and the water-swellable agent  
17       containing chamber is provided with a semipermeable plug; wherein the plug  
18       is releasable from the reservoir at an internal pressure that is lower than the  
19       maximum osmotic pressure generated by the water-swellable agent.

20

21       11. An implantable fluid-imbibing active agent delivery system  
22       comprising an impermeable reservoir and containing a piston that divides the  
23       reservoir into an active agent containing chamber and a water-swellable  
24       agent containing chamber, wherein the active agent containing chamber is  
25       provided with a back-diffusion regulating outlet and the water-swellable agent  
26       containing chamber is provided with a semipermeable plug; wherein the outlet  
27       is releasable from the reservoir at an internal pressure that is lower than the  
28       maximum osmotic pressure generated by the water-swellable agent.

29

30       12. A fluid-imbibing implantable active agent delivery system for  
31       delivering an active agent to a fluid environment of use for a predetermined

1 administration period, wherein the time to start-up is less than 10% of the  
2 predetermined administration period.

3

4       13. A method for preparing a fluid-imbibing implantable active agent  
5 delivery system for delivering an active agent to a fluid environment of use for  
6 a predetermined administration period said method comprising injection  
7 molding a semipermeable plug into the end of an impermeable reservoir such  
8 that the semipermeable plug is protected by the reservoir.

9

10      14. An implantable active agent delivery system for delivering an  
11 active agent to a fluid environment of use, said agent being susceptible to  
12 degradation if exposed to the fluid environment of use prior to delivery, said  
13 system comprising:

14       (a) a piston that divides the system into a first and second chamber,  
15 the first and second chambers each having an open end;  
16       (b) a water-swellable agent formulation in the first chamber;  
17       (c) an active agent formulation in the second chamber;  
18       (d) a semipermeable plug in the open end of the first chamber; and  
19       (e) a back-diffusion regulating outlet in the open end of the second  
20 chamber;

21       wherein said system effectively seals the active agent chamber and  
22 isolates it from the environment of use.

23

24      15. A back-diffusion regulating outlet useful in an active agent  
25 delivery system for delivering active agent to a fluid environment of use, said  
26 outlet defining a flow path wherein the length, interior cross-sectional shape  
27 and area provide for an average linear velocity of the active agent that is  
28 higher than the linear inward flux of the fluid environment of use.

29

30      16. The outlet of claim 15 wherein the flow path is helical in shape.

31

1        17. A semipermeable plug useful in an active agent delivery system  
2 for delivering an active agent to a fluid environment of use, said plug being  
3 water-swellable and expanding linearly in said delivery system to commence  
4 pumping of active agent upon insertion of the delivery system in the fluid  
5 environment of use.

6

7        18. The device of any of claims 1 or 13 wherein the semipermeable  
8 material is selected from the group consisting of plasticized cellulosic  
9 materials, polyurethanes and polyamides.

10

11        19. The device of any of claims 1, 6, 8 or 14 wherein the active  
12 agent is selected from the group consisting of a protein, a peptide or a gene  
13 therapy agent.

14

15        20. The device of claim 19 wherein the active agent is an LHRH  
16 agonist or antagonist.

17

18        21. The device of claim 19 wherein the active agent is leuprolide.

19

20        22. The device of claim 19 wherein the active agent is selected from  
21 the group consisting of Factor VIII and Factor IX.

22

23        23. The device of any of claims 1, 6 or 8 wherein the active agent is  
24 delivered to a site remote from the device.

25

26        24. An implantable leuprolide delivery system comprising:  
27            (a) an impermeable reservoir;  
28            (b) a piston that divides the reservoir into a first and a second  
29 chamber, the first and second chambers each having an open end;  
30            (c) a water-swellable agent formulation in the first chamber;  
31            (d) a leuprolide formulation in the second chamber;

1                 (e)    a semipermeable plug in the open end of the first chamber; and  
2                 (f)    a back-diffusion regulating outlet in the open end of the second  
3    chamber;

4                 wherein the system effectively seals the second chamber and isolates  
5    the leuprolide formulation from the environment of use.

6

7                 25.    The system of claim 24 wherein the reservoir is titanium or a  
8    titanium alloy.

9

10                26.    The system of claim 24 wherein the piston is formed of C-Flex®  
11    TPE.

12

13                27.    The system of claim 24 wherein the water-swellable agent  
14    formulation contains at least about 64 mg NaCl.

15

16                28.    The system of claim 24 wherein the water-swellable agent  
17    formulation contains NaCl, a gelling osmopolymer and granulation and  
18    processing aids.

19

20                29.    The system of claim 24 further comprising an additive in the first  
21    chamber.

22

23                30.    The system of claim 29 wherein the additive is PEG 400.

24

25                31.    The system of claim 24 wherein the leuprolide formulation is  
26    leuprolide acetate dissolved in DMSO at an assayed content of 37%  
27    leuprolide.

28

29                32.    The system of claim 24 which contains 65 mg leuprolide.

30

1       33. The system of claim 24 wherein the semipermeable plug is  
2 formed of polyurethane material with 20% water uptake.

3

4       34. The system of claim 24 wherein the back-diffusion regulating  
5 outlet is made of polyethylene and has a flow path helical in shape with a  
6 diameter between 0.003 and 0.020 inches and a length of 2 to 7 cm.

7

8       35. The system of claim 24 which delivers about 0.35 µL leuprolide  
9 formulation per day.

10

11       36. The system of claim 35 which provides continuous delivery of  
12 leuprolide formulation for about one year.

13

14       37. The system of claim 24 which reaches at least about 70%  
15 steady-state delivery by day 14.

16

17       38. The system of claim 24 which delivers about 150 µg leuprolide  
18 per day.

19

20       39. A method of treating a subject suffering from prostatic cancer  
21 comprising administering at least one system of claim 24.

22

23       40. An implantable leuprolide delivery system comprising:  
24           (a) a titanium alloy reservoir;  
25           (b) a C-Flex® TPE piston that divides the reservoirs into a first and  
26 a second chamber, the first and second chambers each having an open end;  
27           (c) a compressed NaCl-based osmotic engine and a PEG additive  
28 in the first chamber;  
29           (d) 65 mg leuprolide as a leuprolide acetate solution in DMSO in  
30 the second chamber;

- 1           (e)     a semipermeable polyurethane plug with 20% water uptake in
- 2     the open end of the first chamber; and
- 3           (f)     a polyethylene back diffusion regulating outlet with a helical flow
- 4     path in the open end of the second chamber;
- 5                 wherein the system continuously delivers about 150 µg leuprolide per
- 6     day for about one year after subcutaneous implantation.

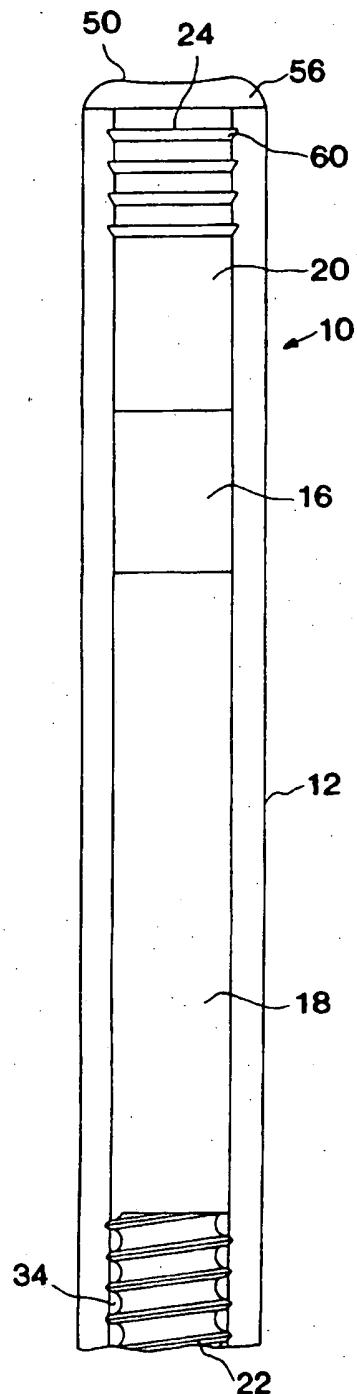


FIG. 1

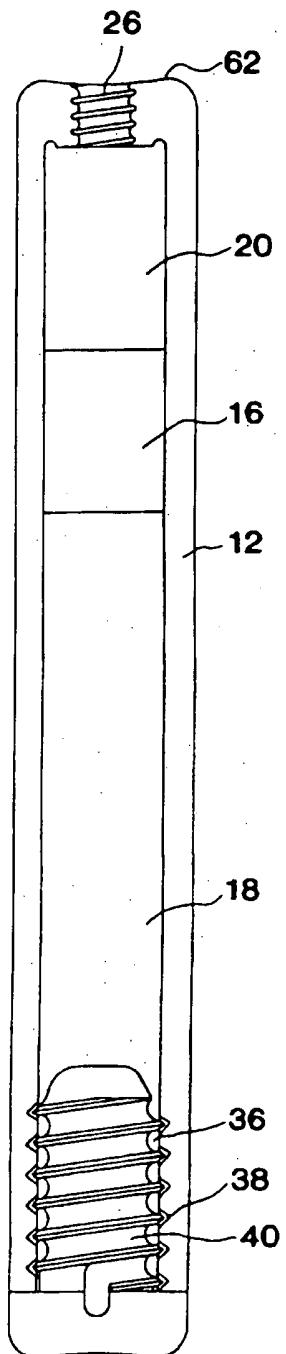


FIG. 2

2 / 6

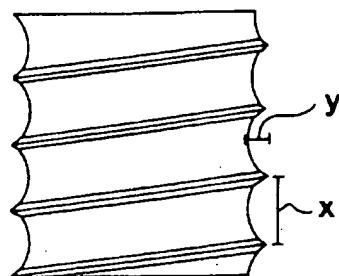


FIG. 3

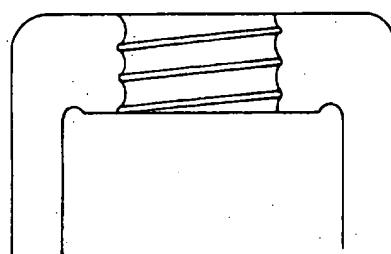


FIG. 7

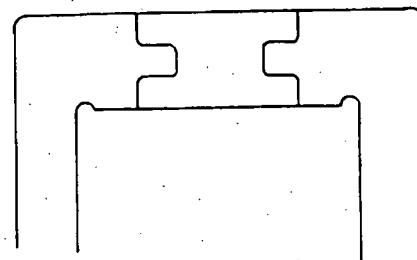


FIG. 8

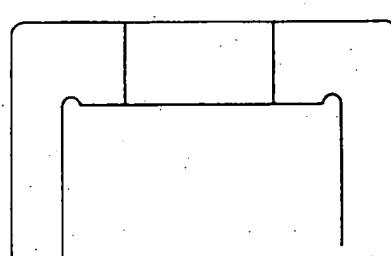


FIG. 5

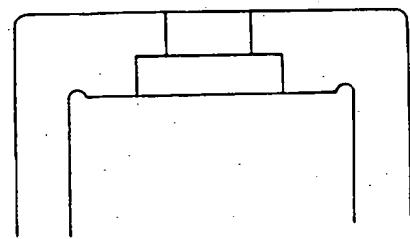


FIG. 6

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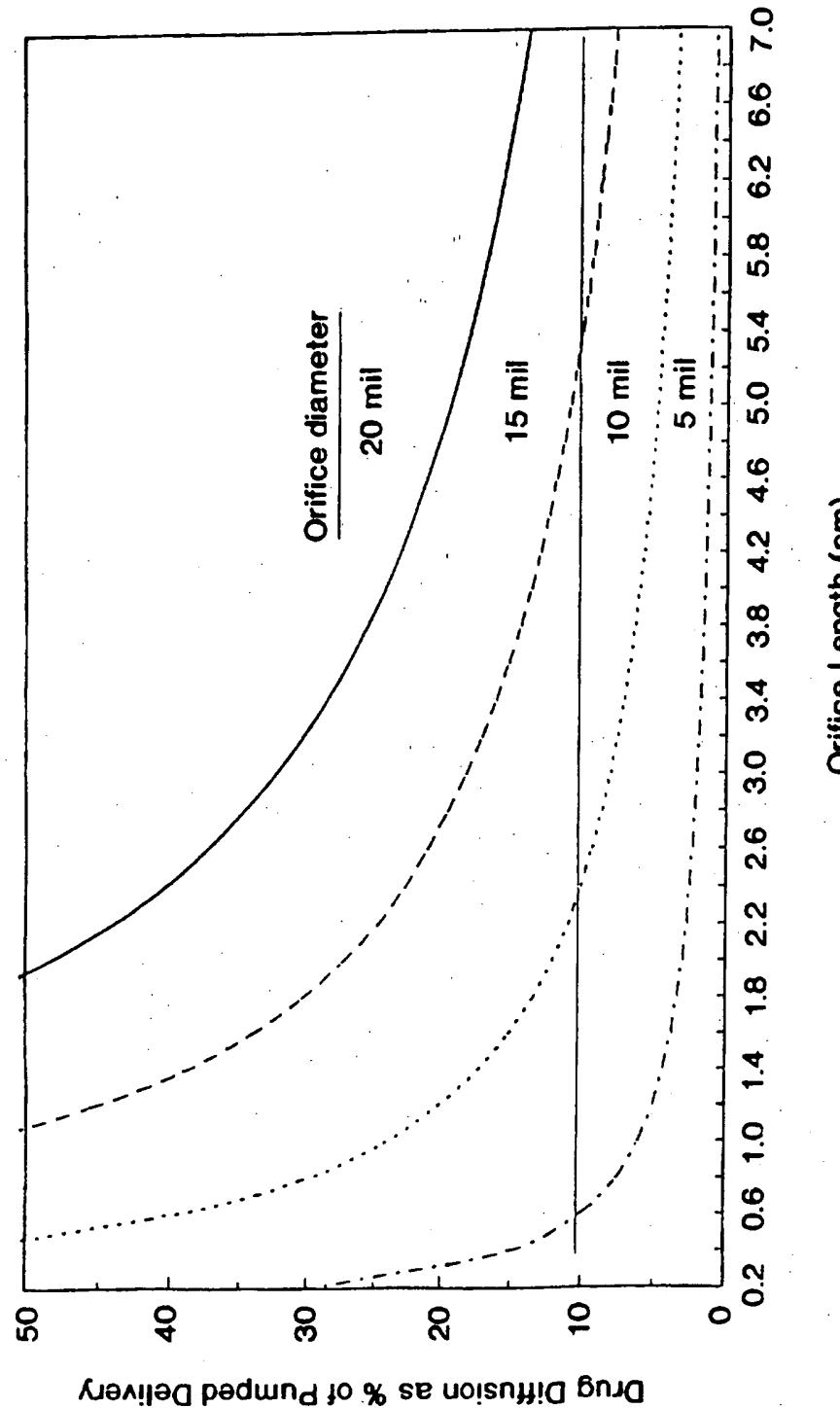


FIG. 4  
Orifice Length (cm)

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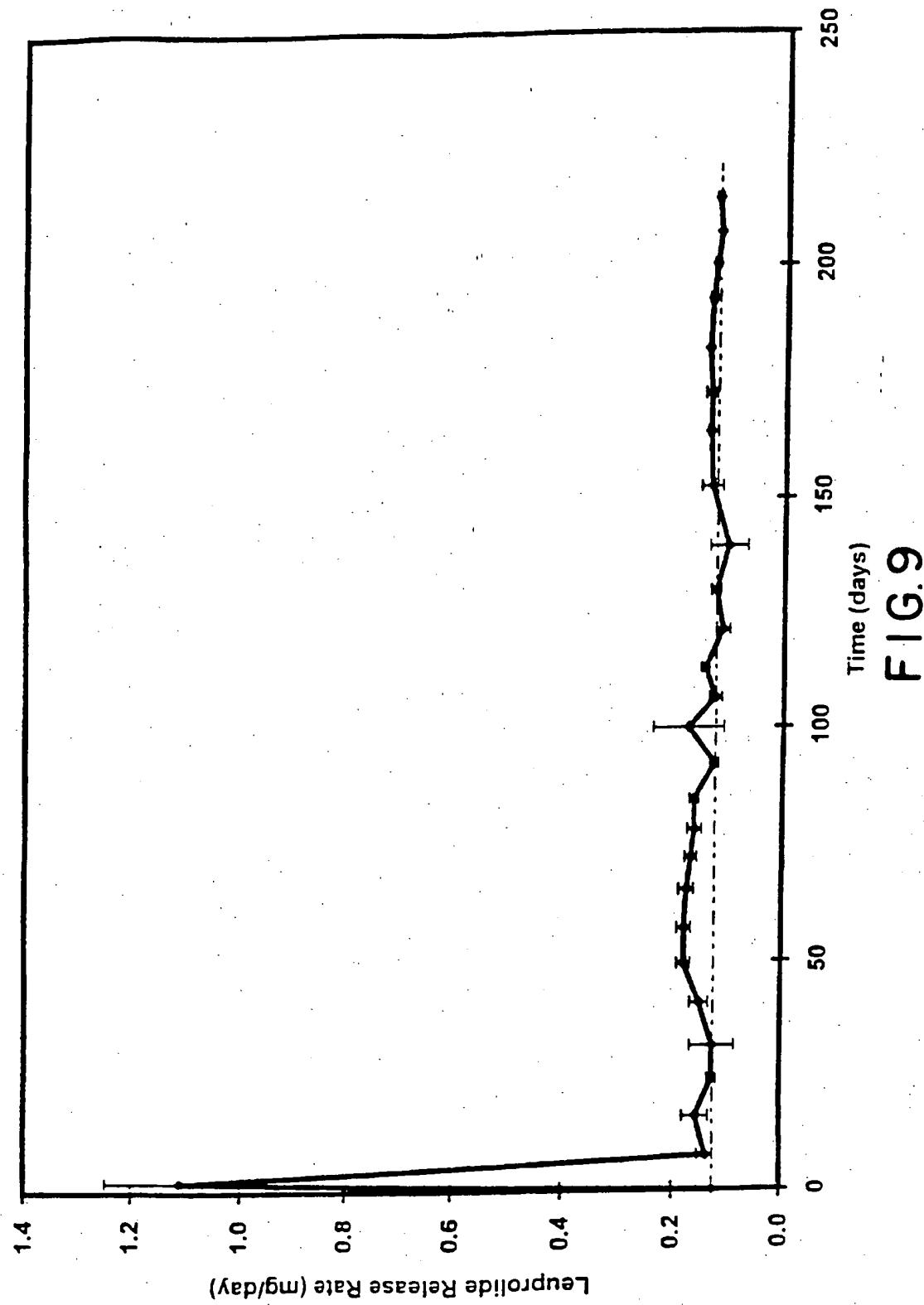


FIG. 9

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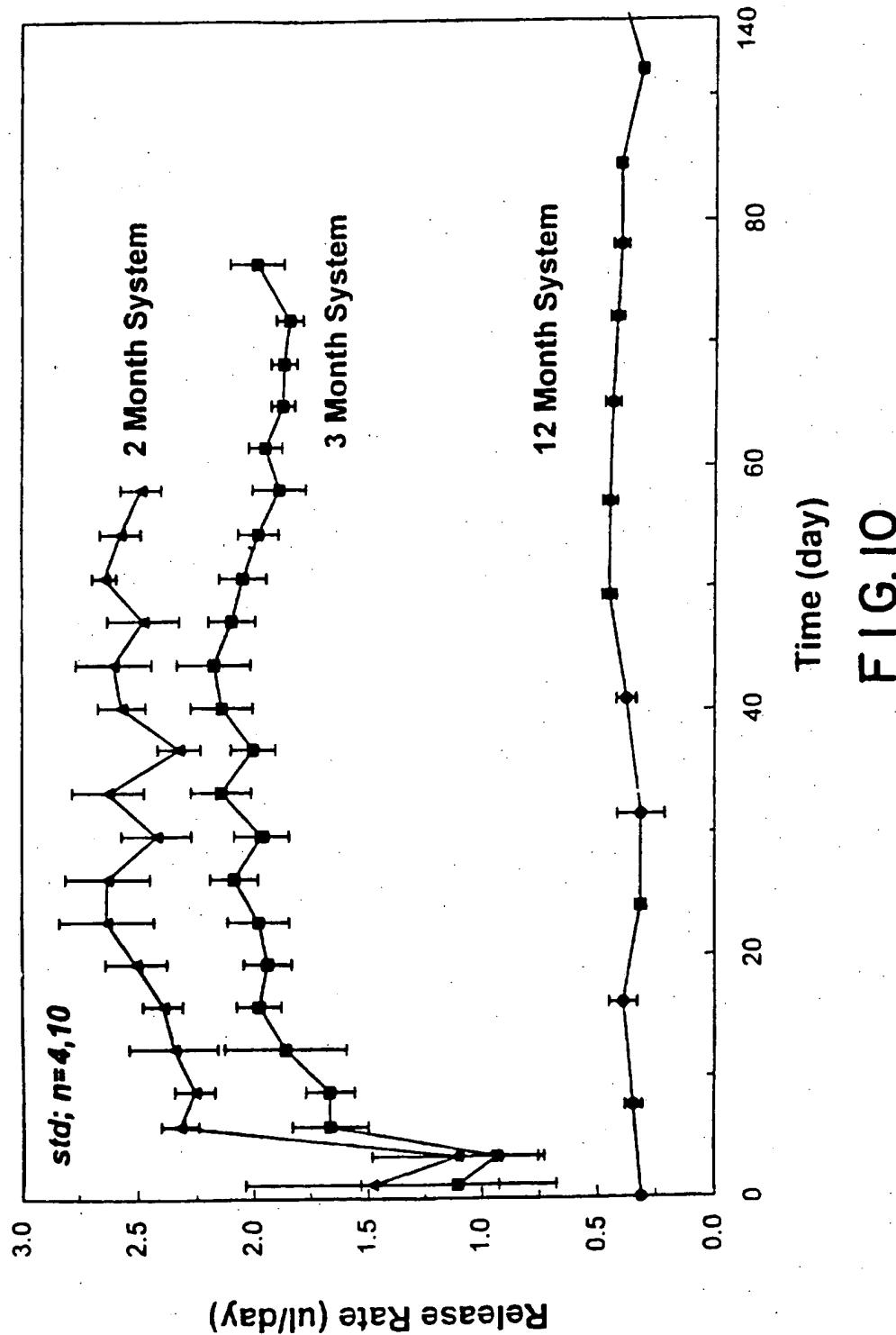


FIG. 10

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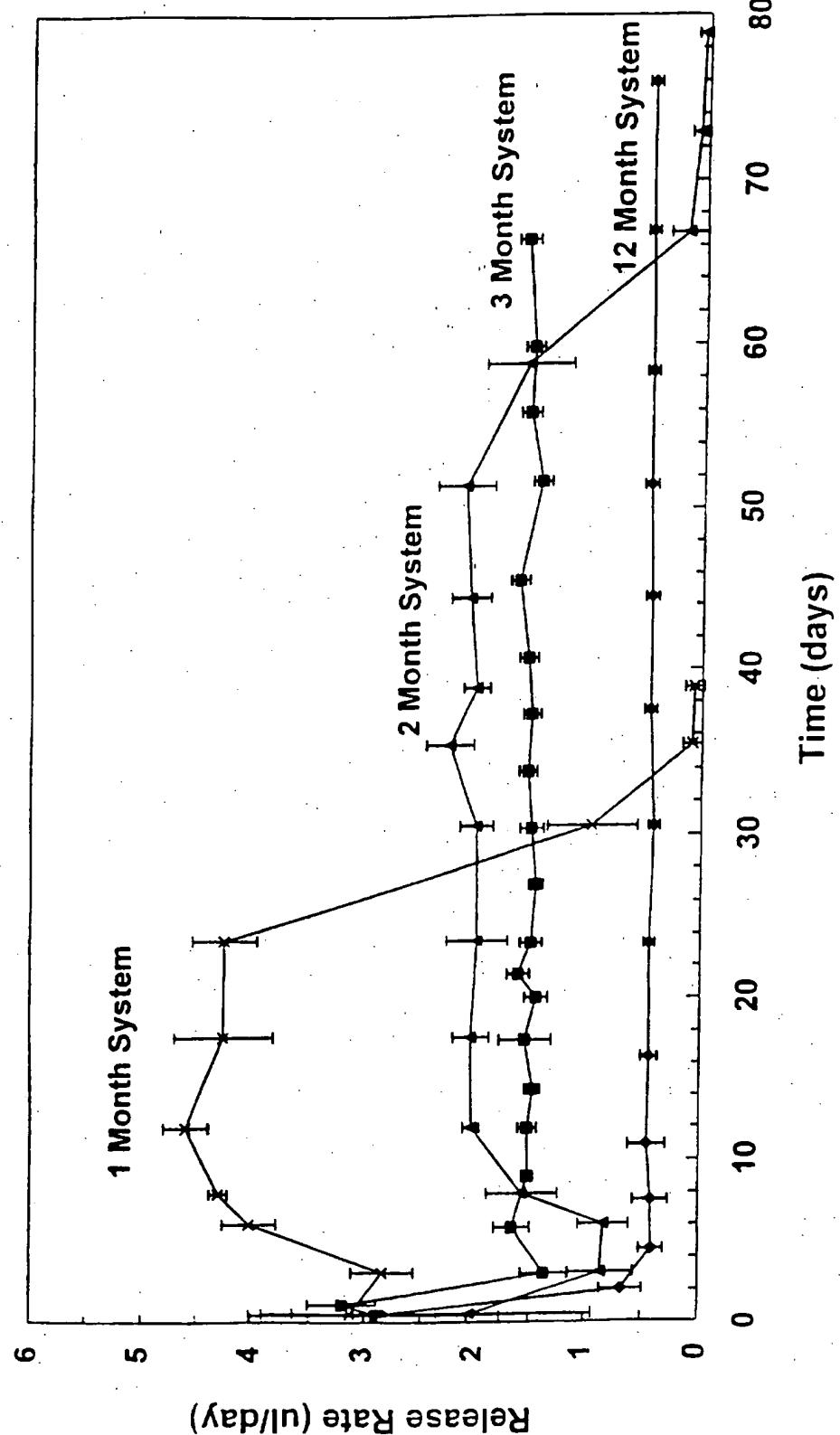


FIG. II

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 97/00722

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 373 867 A (ALZA CORPORATION) 20 June 1990 see the whole document -----	1-39
A	EP 0 627 231 A (ALZA CORPORATION) 7 December 1994 -----	1-39

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

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1

Date of the actual completion of the international search

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/00722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 373867 A	20-06-90	US 5034229 A AU 633514 B AU 4247889 A CA 1331328 A DE 68910290 D DE 68910290 T ES 2045474 T IE 62142 B JP 2184619 A JP 2532692 B NO 174878 B US 5630808 A US 5174999 A US 5057318 A US 5037420 A US 5110596 A US 5135523 A US 5059423 A US 5320616 A	23-07-91 04-02-93 21-06-90 09-08-94 02-12-93 17-02-94 16-01-94 14-12-94 19-07-90 11-09-96 18-04-94 20-05-97 29-12-92 15-10-91 06-08-91 05-05-92 04-08-92 22-10-91 14-06-94
EP 627231 A	07-12-94	US 5308348 A US 5456679 A	03-05-94 10-10-95

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